HHS SBIR RFA-DA-15-001

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The official link for this solicitation is: http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-15-001.html

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Department of Health and Human Services

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Topic Number:
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Description:
Purpose

The purpose of this initiative is to incentivize small businesses to generate tools and products specifically for monitoring and manipulating covalently modified eukaryotic mRNAs and regulatory RNAs.
Background

Covalent chemical modifications can play a crucial role in regulation of biological processes. For example, post-translational modifications such as phosphorylation and lipidation are critically important for regulating protein functions. Similarly, modifications to histone proteins and to DNA itself are critical for epigenomic regulation of gene expression.

Some covalent RNA modifications such as 5'mRNA capping, alternative splicing, and polyadenylation have been well studied, however the functional roles of many covalent RNA modifications are poorly understood. The RNA Modification Database indicates that there are at least 65 RNA modifications that occur in eukaryotic cells. Transfer and ribosomal RNA can be heavily modified, however a number of these covalent modifications also occur in messenger RNA. For example, recent studies have identified N6-methyladenosine sites in thousands of human mRNAs and suggest that this modification may play a role in regulation of alternative splicing and gene expression. It also appears that this RNA methylation mechanism is important in regulating the circadian clock. Interestingly, the FTO gene has been found to enzymatically demethylate N6-methyladenosine in

RNA. FTO was originally identified in a human obesity genome-wide association study and is expressed in the hypothalamus. FTO also appears to regulate the demethylation of mRNAs leading to alterations in dopamine function in the midbrain and striatum. Although the functions of N6-methyladenosine are becoming clearer, the relevance and function of other naturally occurring RNA modifications are poorly understood. Furthermore, oxidative processes may generate covalent RNA modifications that are associated with disease states or aging.

RNA editing is a process in which certain RNAs are modified by adenosine deaminases (ADARs). ADAR post-transcriptional editing can modify adenosine to inosine, leading to alterations in translated proteins that are not coded for by our DNA genomes. ADAR isoforms are expressed dynamically during brain development and ADAR loss can lead to deficits in synaptic function. RNA editing might enable neurons and glia to modify their properties in response to energy fluctuations or environmental changes. Some researchers have linked the editing of serotonin 2C and TPH2 mRNAs to psychiatric diseases. The extent to which RNA editing occurs in small or long non-coding regulatory RNAs is poorly described, but could potentially impact their regulatory functions.

Additionally a novel class of RNAs, the circular RNAs, have recently been discovered in the brain and other tissues. It appears that a circular splicing mechanism may be used to convert linear RNAs into RNA circles. Although the functions of circular RNAs are not well understood, there is evidence that some circular RNAs may be able to function as microRNA sponges and thus impact microRNA regulatory pathways.

Research Objectives

Despite the growing interest in and likely importance of RNA modifications, the available tools that scientists have to monitor and manipulate modified RNAs are extremely limited. The purpose of this FOA is to stimulate small businesses to begin to develop robust tools specifically for monitoring and manipulating covalently modified eukaryotic mRNAs and regulatory RNAs to enable the scientific community to effectively explore this new scientific area. In particular, it is hoped that these tools and products for monitoring and manipulating modified RNAs will serve as the foundation for NIDA-relevant research into the potential roles of RNA modifications in both HIV infection/progression as well as into the molecular mechanisms of substance abuse disorders and co-occurring psychiatric disorders.

Two companion FOAs have been released in this scientific area: DA-15-002 describes the R41/R42 mechanism, while this FOA (DA-15-001) describes the R43/R44 mechanism. If the innovative tool to be commercialized will be developed via a partnership of ideas between a small business and an academic/non-profit research institution, the program director/principal investigator should consider applying using the STTR mechanism (R41/R42). Otherwise, small businesses interested in the development of relevant innovative technologies are encouraged to apply via the SBIR mechanism (R43/R44).

Examples of Potential Tools or Products. This initiative will support small business development of research enabling tools and products such as (but not limited to):

- Antibodies or other affinity reagents for detection, quantitation, or immunoprecipitation of modified RNAs, or enzymes that write, erase, or bind to these modifications;
- Assay systems or reagents that facilitate the discovery, detection or quantitation of modified RNAs, circular RNAs, or edited RNAs;
- The development or adaptation of nanoscale sequencing devices or other equipment for identification and quantitation of sequence-specific RNA modifications;
- The development of algorithms or analysis software to facilitate the identification of modified, circular, or edited RNAs from high throughput sequencing datasets; and
- The development of constructs, kits, small molecule, or genetic resources that enable researchers to manipulate modified RNAs to enable investigation into their biological or disease functions.